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Salivary Gland Disorders and Heredity

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From personal observations, I review the genetic disorders of salivary gland development and function, including the lacrimo-auriculodentodigital (LADD) syndrome, autosomal dominant hypoplasia/agenesis of salivary and/or lacrimal glands, chronic recurrent sialadenitis, polycystic-dysgenetic disease of the parotids and salivary calculi. Am. J. Med. Genet. 68:222–224, 1997

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INTRODUCTION

Saliva has many functions; abnormalities of salivary functions, such as "drooling" in the Riley-Day syndrome or familial dysautonomia, or the "sticky" saliva in the Prader-Willi syndrome, are rare. Saliva is a clear, tasteless, odorless, slightly acid (pH 6.8) viscid fluid consisting of the secretions of the sublingual, parotid and submaxillary glands and the mucous glands of the oral cavity. It functions to keep the mucous membranes of the mouth moist, to lubricate food during mastication, and partly to convert starch into maltose through the action of the enzyme ptyalin. Though uncommon, in a long career in pediatric genetics, disorders of salivary gland structure and function are encountered regularly. The following is a brief review of these disorders, at least of those known to be genetic.

Hypoplasia/Agenesis of Salivary Glands

There exists absence (agenesis) or hypoplasia of some or all major salivary glands with or without absence of Stensen's duct, lacrimal glands and/or nasolacrimal ducts and puncta (i.e., with or without alacrima). Familial occurrence of absence of salivary glands (in a father and daughter) was first described by Ramsey [1924]; Blackmar [1925] seems to have been the first to describe congenital absence of the lacrimal puncta with aptyalism and decreased lacrimation; this 11-year-old boy also had severe caries, frequently noted in cases of congenital aptyalism. Some 12 or so reports of this condition [q.v. Wiedemann, 1991] have established this as a complex, pleiotropic autosomal dominant disorder (MIM 180 920).

The LADD Syndrome

The lacrimoauriculodentodigital (LADD), or Levy-Hollister syndrome, is a true multiple congenital anomalies (MCA) syndrome comprising hypoplasia, aplasias or atresias of the lacrimal system, anomalies of the ears and hearing loss, hypoplasias, aplasias or atresias of the salivary system, dental anomalies and digital malformations including absent, hypoplastic or triphalangeal thumbs, anomalies of 2nd, 3rd or 4th digits or of 5th digits and hypothenar areas. This condition appears to have been reported first by Levy [1967] and Hollister et al. [1973, 1974]. This autosomal dominant disorder (MIM 149730) was reviewed by Wiedemann and Drescher [1986]. Affected individuals also have absent or small, peg-shaped lateral maxillary incisors and mild enamel dysplasia and possible renal anomalies (the latter as part of an acrorenal field defect).

Chronic Recurrent Sialadenitis

More common than either of the above conditions is chronic, recurrent sialadenitis. The "register of salivary gland diseases" at the Institute of Pathology at the University of Hamburg lists 1,546 cases of chronic recurrent parotitis and sialoadenitis of the submandibular gland (type Küttner) out of a total of 10,942 cases (1965–1985, Seiffert [1988]). My personal observations include over 30 cases of chronic relapsing sialadenitis.

Chronic recurrent parotitis (with or without simultaneous involvement of the submandibular gland) is a characteristic disorder known for a long time, usually with a bilateral intermittent or fluctuating parotidomegaly. This may occur as an autosomal dominant trait (MIM 168800), and seems to have been described first by von Reuss [1909] as chronic recurrent parotitis in children. Many cases have since been reported. This condition may begin at any time between 1 month up to puberty when it often becomes asymptomatic. More boys than girls are affected. Hereditary cases are not uncommon [Hochschild, 1920: 7 cases in 3 generations;

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Meyer, 1934: 3 cases in 3 generations; Gorter, 1941: father and son; Jones, 1953: 2 cases in 2 generations, and, the only reference in McKusick, Marie et al., 1967: 6 cases in 3 generations]. These cases were reported respectively from Austria, the U.S.A., the Netherlands, the United Kingdom and France.

My personal observations include 2 sibs, a 10-year-old boy and his 12-year-old sister who manifested chronic recurrent parotitis and sialadenitis of the submaxillary glands from early childhood. Three sibs were unaffected. During her childhood, the mother had had chronic recurrent parotitis which decreased in severity after puberty. A familial case that came to my attention in the 1940s is illustrated in Figure 1; all 3 brothers were affected, but the eldest seems to have been in "remission."

The pathogenesis of this disorder is complex. Congenital sialectasia seems to play a role and can be demonstrated by sialography which shows the characteristic appearance of a branching, leafy tree or bush (see Fig. 2 from Wiedemann, 1951). These sialectatic changes are often bilateral, even if clinical manifestations are only unilateral [Gorter, 1941; Bailey, 1945; Smith, 1953; Krepler, 1957; Rauch, 1959; Becker et al., 1960; Seifert, personal communication].

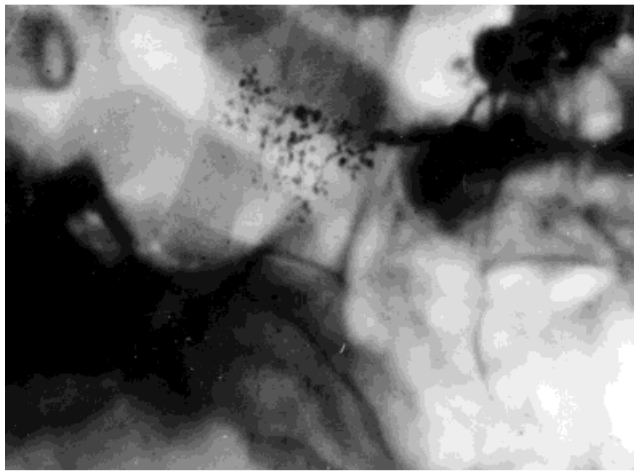

Fig. 2. Sialogramm of a 2-year-old boy with chronic recurrent parotitis, manifested since infancy. Note typical appearance of a "tree in leaf" (sialectases) (Reproduced, with permission, from Wiedemann, 1951).

Polycystic-Dysgenetic Disease of the Parotids

This condition, first delineated by Seifert et al. [1981], is different from chronic recurrent parotitis and must be distinguished from congenital sialectasis of the parotid glands as a separate nosologic entity: in this disorder the cystic changes are due to a malformation of the distal duct system, in particular the processes of branching and canalization. The histopathology of this condition is well-defined, but it seems to be a rare entity [Batsakis et al., 1988]. The 6-year-old girl described by Seifert et al. [1981] had an affected father; thus, polycystic disease of the parotids appears to be an autosomal dominant trait. This disorder may be a human model of a defect of interaction between activin, follistatin and TGF-β known to disrupt epithelial branching morphogenesis in developing glandular tissue in the mouse, including salivary glands, pancreas and ureteric branching in kidneys [Ritvos et al., 1995].

Fig. 1. Three boys, at age 9, 6½ and 14 years (from left to right) with chronic recurrent parotitis; the 14-year-old boy is in intermission. Two elder sisters are unaffected.

Salivary duct calculi are usually sporadic events; however, Bullock [1982] reported on chronic calculous parotitis beginning at age 12 months in a girl with a history of parotid calculi in the mother and submandibular calculi in the maternal grandmother (MIM 181010).

Diffuse and often recurrent enlargement of the submandibular glands (more so than of the parotids) may be a manifestation in cystic fibrosis, in the sense of a sialadenosis [Rauch, 1959]. Recurrent parotid swelling may be an initial sign in Sjögren syndrome [Mizuno et al., 1989; Hara et al., 1992; MIM 270150].

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